IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Examiner	: Maria Marvich	
Serial No.	: 10/764,628	
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Inventors	: Véronique Trochon-Joseph	Docket No.: 1002-04
	: He Lu	
	: Claudine Soria	Confirmation No.: 9953
Title	: METHOD OF INHIBITING	
	: ANGIOGENESIS OR	
	: INVASION OR FORMATION	
	: OF METASTASES	

DECLARATION OF PIERRE ATTALI UNDER RULE 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir :

I, Pierre ATTALI, residing at 2 rue du lieutenant Heitz, F-94300 Vincennes ; (France), declare and say that:

I am citizen of France.

I am MD, MSc, and have a long experience in clinical development and have been Head of the Clinical Research Department of a major international pharmaceutical industry for 8 years. I am currently Chief Operating Officer, Strategy & Medical Affairs of BioAlliance Pharma, and I also practice in academic hospitals where I have consultations and act as principal investigator in several clinical trials in liver diseases.

I am familiar with the content of US Patent Application Serial No. 10/764,628.

I have been informed that, in the AMEP electrotransfer biotherapy, it is considered that the intramuscular route of administration would lead to unpredictable results in human. As a consequence, AMEP electrotransfer biotherapy is liable to be performed in humans by intratumoral route of administration only.

This analysis is in contradiction with the preliminary opinion of the committee of experts of the French drug agency (AFSSAPS) when the rationale of the AMEP electrotransfer biotherapy was first disclosed to them in the process of obtaining authorisation of phase I/II clinical trial.

The committee considered that the preclinical data obtained by intramuscular electrotransfer of AMEP plasmid in mice suggested a systemic effect of the AMEP plasmid when administered in the muscle. This was confirmed by in-house analysis which showed that AMEP protein is detected in circulating blood of mice intramuscularly electrotransfered with AMEP plasmid.

Although the committee acknowledged the scientific rationale behind a first local administration in a human, by intratumoral route, the committee's initial opinion was that the administration in humans should rather be made by the intramuscular route. Experts of the committee indeed considered that intramuscular electrotransfer of AMEP plasmid would ensure sustained expression and systemic action of the AMEP protein. By an intratumoral route, expression of AMEP protein could progressively decrease to extinction due to transformed tumor cell death, thereby possibly reducing long term treatment efficacy.

Nevertheless, for the needs of phase I clinical trial, an intratumoral route was selected for the first administration in humans for safety reasons, to optionally remove the electrotransfered tumor should a serious adverse event occur in a patient.

A Phase I clinical trial is ongoing, with four patients with metastatic melanoma included in the safety study so far. Up to now, the follow-up of one of the patients has shown stabilization in the size of the treated lesion just after treatment. At day 22 after electrotransfer, the size of the treated lesion was stabilized compared to baseline and uptake of contrast agent reduced in contrast echography, indicating reduction of vascularization in the treated lesion compared to the baseline. This result demonstrates efficacy of the treatment in humans even at the very low dose of AMEP plasmid currently administered to establish safety of the treatment.

The undersigned Declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed on May 9th, 2011

Pierre ATTALI